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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,054	07/02/2007	**Julian P. Whitelegge**	67789-599	5324

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EXAMINER	
RIDER, LANCE W	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/597,054	WHITELEGGE ET AL.	
	Examiner	Art Unit	
	LANCE RIDER	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/20/2006 and 03/25/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-23 are currently pending.

Information Disclosure Statement

The Information Disclosure Statements (IDS)s, filed by applicant on October 20th 2006 and March 25th 2008 have been considered by the examiner in the present case.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims of the instant application recite a limitation of "analyzing said subtle isotope modification with the Isosolv algorithm". In the example 7 it is mentioned that the data is analyzed with the Isosolv algorithm and one of the formulas used in this algorithm is recited, but the rest of the algorithm's or parameters Isosolv uses are absent. There is a mention of Isosolv incrementally altering the estimated ^{13}C

abundance parameters and minimizing the error between the calculated and actual ^{13}C distributions, but no statement of how this is accomplished is provided. It is also stated that Isosolv includes natural minor contributions of D, ^{15}N, and $^{17/18}O$, but no mention of how these are included. While such information can indirectly provide information regarding how one could create an algorithm to calculate an isotope ratio from a peptide distribution as stated in example 7, no indication as to the exact methods necessary to achieve this calculation are given. The claims make no clear statement of the exact functions Isosolv runs, or many of the algorithms supposedly used in its calculation of an isotope ratio. Applicant is trying to claim the use of a particular algorithm (that is, a series of mathematical steps) in a method of performing expression proteomic analysis. But Applicant has kept the nature of this algorithm hidden. Example 7 shows a calculation of the C-13 probability "P" using the function prob(n)=combin(X,n)*Pn*(1-P)(X-n), wherein n is the number of C-13 atoms, X is the total number of carbons. The specification, including the example, does not indicate what the function "combin" is. Nor is it clear what "Pn" or "prob(n)" are. If "Pn" is the probability of "n" then what is "prob(n)"? Furthermore, while the example states that Isosolv takes into account the isotopic distribution of ^{15}N, D, $^{17/18}O$, the example does not indicate how Isosolv does that. Because the Applicant does not disclose what mathematical steps must be taken to undertake the invention, the claims fail to meet the written description requirement.

Therefore, the specification provides insufficient written description for “analyzing said subtle isotope modification with the Isosolv algorithm" as claimed in the instant

application. Applicant has not provided an adequate description as to how Isosolv functions.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim1-6, 8-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites a limitation of “subtle". In the specification of the instant application subtle is described as follows:

"Subtle," as used herein with reference to the modification of isotopes included in target molecules, is defined as a "swapping" of, on average, an amount of isotopes included in target molecules such that there is a measurable effect upon the observed peptide isotope distribution, without causing a gross extension or displacement 'of the single isotope envelope. The modification introduced is gross compared to natural isotopic variability yet subtle compared with strategies that seek full exchange.” The application does not indicate how much the isotope distribution must change for the change to be "subtle" as claimed. The artisan would not know how much change is too much to be “subtle”. Nor would the artisan know if there is any minimum amount of change required before the change is "subtle." Because the artisan would not know the metes and bounds of this term, the claims are indefinite. The remaining claims are

Deleted: ¶

rejected for ultimately depending on claim 1 without clarifying this issue. Claim 7 is not included in this rejection, because claim 7 requires a distinct range of modification.

Claims 19-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

All of these factors have been considered, and the most relevant are discussed below.

The breadth of the claims

The claims encompass methods for performing proteomic expression analysis by providing a sample in which a “subtle” isotope modification has been induced and analyzing the “subtle” isotope modification using the “Isosolv” algorithm. The limitation of providing a sample in which a “subtle” isotope modification has been induced concerns almost any sample in existence given the unclear definition of “subtle” as stated above. Further a “subtle” modification can occur even in nature as plants and animals from different regions of the earth can have different isotopic distributions given their geographic location. The limitation of analyzing using the “Isosolv” algorithm is limited to the use of a specific program (set of mathematical formula). The identity of the specific steps "Isosolv” performs are not clearly defined in the art, specification, or claims. As such the breadth of this limitation cannot be clearly defined.

The state of the prior art

The article by Whitelegge, J.P., et al., (Phytochemistry, 2004, **presented in the IDS**) is the only prior art of record discussing isosolv. The article copies verbatim the disclosure in the specification. The art teaches no more than the specification about the

nature of isosolv.

The amount of direction provided by the inventor

The inventor discloses the use of the "Isosolv" program in example 7 of the specification. In this example a calculation of the C-13 probability "P" using the function prob(n)=combin(X,n)*Pn*(1-P)(X-n), wherein n is the number of C-13 atoms, X is the total number of carbons is disclosed. The specification, including the example, does not indicate what the function "combin" is. Nor is it clear what "Pn" or "prob(n)" are. If "Pn" is the probability of "n" then what is "prob(n)"? Furthermore, while the example states that Isosolv takes into account the isotopic distribution of ^{15}N, D, $^{17/18}O$, the example does not indicate how Isosolv does that. No other teachings are present in the art for this program. No further explanation as to how this algorithm functions is found in the specification, and the prior art is equally silent as to the steps this algorithm performs.

The existence of working examples

Example 7 shows a calculation of the C-13 probability "P" using the function prob(n)=combin(X,n)*Pn*(1-P)(X-n), wherein n is the number of C-13 atoms, X is the total number of carbons. The specification, including the example, does not indicate what the function "combin" is. Nor is it clear what "Pn" or "prob(n)" are. If "Pn" is the probability of "n" then what is "prob(n)"? Furthermore, while the example states that Isosolv takes into account the isotopic distribution of ^{15}N, D, $^{17/18}O$, the example does not indicate how Isosolv does that.

The quantity of experimentation needed to make or use the invention

The claims require a step of using the "Isosolv" algorithm, but the specification does not disclose what this algorithm is. Nor are the details of "Isosolv" known in the art. To practice the invention, the artisan would have to use an algorithm that is unknown to the artisan. The artisan cannot carry out an algorithm (that is, a series of mathematical steps) unless the artisan knows what those steps are. Because the artisan does not know what "Isosolv" is, the artisan could not practice the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8 and 10-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Ford, G.C., et al., (Biomedical Mass Spectrometry, 1985).

Ford, G.C., et al., (Biomedical Mass Spectrometry, 1985) discloses in the abstract, methods and systems for determining the concentration and isotope enrichment of ^{13}C leucine in human (a mammal), and that the isotope enrichment is introduced through the diet of the individuals. The enrichment is analyzed by mass spectrometry (an analytic tool) in which protein turnover is monitored and the enrichment concentration of the ^{13}C over the natural ^{12}C is 0.5% and 0.2% which meets

the limitations of a subtle effect with a ^{13}C:^{12}C isotope ratio change of about 100:1 to 200:1. The analytical tool of Ford is “configured" to measure isotope ratios of leucine, meeting the limitation of claim 3

The recitation of the limitation of “performing expression proteomic analysis” has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Claims 1, 3, 4, 6, 8-10, 12, 15, 17, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Ong, S., et al., (Molecular and Cellular Proteomics, 2002)

Ong, S., et al., (Molecular and Cellular Proteomics, 2002) discloses in the abstract and experimental procedures, methods and systems to perform stable isotope expression analysis of proteins with deuterated leucine. On page 377, paragraphs 6 and 8, it is disclosed that 99% deuterium labeled and unlabeled leucine are used to isotopically label protein samples in mammalian cells and mixed together at concentrations of 1:1:, 1:3. On page 377, in paragraph 9, it is disclosed that the proteins were analyzed by MALDI-TOF mass spectrometry. On page 37, paragraph 9, the ratios

of the isotopic distributions of peptides are determined. The method used in this paper is disclosed in the title of the publication as SILAC.

The recitation of the limitation of "performing expression proteomic analysis" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Claims 1-3, 6, 8-12, 15, and 17-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Pasa-Tolie, et al., (JACS, 1999).

Pasa-Tolie, et al., (JACS, 1999) discloses throughout the disclosure methods and systems for performing proteomic expression analysis. Pasa-Tolie, et al., (JACS, 1999) discloses on page 7949, paragraphs 5 and 6, the subtle modification of the stable isotopes of an organism by depleting ^{13}C, ^{15}N, and ^{2}H by growth in a stable isotope medium (^{12}C etc., are stable isotopes). The natural abundance of these isotopes is very low, so the change in their abundance is 1% or less, thus subtle. On page 7950, in paragraph 2, it is disclosed that the proteins from these depleted organisms are analyzed by mass spectrometry, thereby determining their levels, which is an inherent

measure of their turnover. On page 7950, in paragraph 4, the use of this technique with MSMS is disclosed.

Claims 1-3, 6, 8-12, 15, and 17-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Oda, Y., et al., (PNAS, 1999).

Oda, Y., et al., (PNAS, 1999) discloses throughout the disclosure methods and systems for performing proteomic expression analysis. Oda, Y., et al., (PNAS, 1999) discloses on page 6591 (last paragraph), and page 6592 (first paragraph), the labeling of yeast cells with ^{15}N by growth in a stable isotope medium with 99.6% labeling. On page 6592, paragraphs 3 and 4, the analysis of the modifications by mass spectrometry are disclosed. In the first paragraph of the "results and discussion" an expression analysis, which determines the proteins levels, is disclosed. This expression analysis is an inherent measure of their turnover. On page 6593, paragraph 1, and figure 3, disclose measuring and calculating isotope distributions. On page 6591, in the "data processing" section the use of MSMS is disclosed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ford, G.C., et al., (Biomedical Mass Spectrometry, 1985) in view of Oda, Y., et al., (PNAS, 1999).

Ford, G.C., et al., (Biomedical Mass Spectrometry, 1985) discloses, in the abstract, methods and systems for determining the concentration and isotope enrichment of ^{13}C leucine in human (a mammal) plasma, by mass spectrometry (an

analytic tool) in which protein turnover is monitored and the enrichment concentration of the ^{13}C over the natural ^{12}C is 0.5% and 2%.

Ford performs an analysis on a single amino acid, but does not analyze turnover of a peptide or protein. Nor does Ford use MSMS for the analysis. Ford only uses MS.

Pasa-Tolie, et al., (JACS, 1999) discloses, throughout the disclosure, methods and systems for performing proteomic expression analysis using stable isotopes for specific proteins. Pasa-Tolie analyzes microorganisms, but recognizes that the technique is applicable and useful as a diagnostic tool for higher order organism, such as mammals and humans. In order to analyze proteins, Pasa-Tolie uses a MSMS technique. MSMS is a type of mass spectrometry, but is different from the "standard" mass spectrometry discussed in Ford.

It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to use MSMS in performing protein expression analysis on human protein samples. Doing so would be following the express suggestion of Pasa-Tolie, who indicates that this technique would be useful in higher organisms. Ford shows that related techniques have been used successfully in humans. Thus, the artisan would enjoy a reasonable expectation of success.

Conclusion

No claims are currently allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LANCE RIDER whose telephone number is (571)270-1337. The examiner can normally be reached on M-F 11-12 and 1-4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LANCE RIDER/
Examiner, Art Unit 1618

/Eric E Silverman/
Primary Examiner, Art Unit 1618